Intravenous Lipid Emulsions for Parenteral Nutrition: What Choices Do We Have?

Cynthia L. Lieu, Pharm.D., BCNSP
Nutrition Support Pharmacist, LAC+USC Medical Center
Associate Professor of Clinical Pharmacy
University of Southern California – School of Pharmacy
CLLLieu@usc.edu or Cynthia.Lieu@usc.edu
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• I will be discussing:
  – Off labeled indications
  – Products that are not currently FDA approved
• I have no financial disclosures
Learning objectives

Pharmacist:
• Compare & contrast the components of various types of intravenous lipid emulsions
• Select individuals who might benefit from the use of alternative intravenous lipid emulsions
• Evaluate individuals for potential adverse effects associated with specific types of lipid emulsions

Technician:
• Compare the components of various types of intravenous lipid emulsions
• Discuss sources of intravenous omega-3, omega-6, and omega-9 fatty acids
• Identify potential adverse effects with specific types of intravenous lipid emulsions
Abbreviations

- EN: enteral nutrition
- PN: parenteral nutrition
- HPN: home parenteral nutrition
- IVFE: intravenous fat emulsion
- IVLE: intravenous lipid emulsion
- LCT: long-chain triglycerides
- MCT: medium-chain triglycerides
- EFAs: essential fatty acids
- EFAD: essential fatty acid deficiency
- MUFAs: monounsaturated fatty acids
- PUFAs: polyunsaturated fatty acids
- LC-PUFAs: long-chain polyunsaturated fatty acids
- LA: Linoleic acid
- ALA: α-Linolenic acid
- EPA: eicosapentaenoic acid
- DHA: docosahexaenoic acid
- AA: arachidonic acid
- FO: fish oil
- OO: olive oil
- SO: soybean oil
- BG: blood glucose
- TG: triglycerides
- LFTs: liver function tests
- AP: alkaline phosphatase
- AST: aspartate aminotransferase
- ALT: alanine aminotransferase
- CB: conjugated bilirubin
- DB: direct bilirubin
- TB: total bilirubin
- PNAC: parenteral nutrition-associated cholestasis
- PNALD: parenteral nutrition-associated liver disease
- IFALD: intestinal failure-associated liver disease
Self-assessment question # 1

• Olive oil is a rich source of ____.
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 2

• Which of the following products contains the lowest amount of phytosterols?
  A. Clinoleic
  B. Intralipid
  C. Omegaven
  D. SMOFlipid
Self-assessment question # 3

• For individuals who develop parenteral nutrition-associated cholestasis, the current practice is to reduce the amount of ____ administered.
  
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 4

• Individuals with significant inflammation may benefit the most from the use of intravenous lipid emulsions which contain ____.
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 5

• Which micronutrient is added to intravenous lipid emulsions for its antioxidant effects?
  A. Selenium
  B. Vitamin A
  C. Vitamin C
  D. Vitamin E
Omega-3 FA Precursors

- Weak Inflammatory Eicosanoids
- 3-Series Prostaglandins
- 3-series Thromboxanes
- 5-series Leukotrienes

Eicosapentaenoic Acid (EPA)

Pro-resolving mediators of inflammation
- E-series Resolvins
- Lipoxins

Docosahexaenoic Acid (DHA)

Pro-resolving mediators of inflammation
- D-series Resolvins
- Lipoxins

Omega-6 FA Precursors

- Potent Inflammatory Eicosanoids
- 2-Series Prostaglandins
- 2-series Thromboxanes
- 4-series Leukotrienes

Arachidonic Acid (AA)

Anti-inflammatory Epoxyeicosatrienoic Acids (EETs)
Pause Point:

What are reasons why you use Intravenous Lipid Emulsions (IVLEs)?

What potential adverse effects concern you with the use of Intravenous Lipid Emulsions (IVLEs)?
Intravenous Lipid Emulsions (IVLEs)

- Component of parenteral nutrition (PN)
- Concentrated source of calories
- Reduce requirement for dextrose
- Essential fatty acids (EFAs) & long-chain polyunsaturated fatty acids (LC-PUFAs)
  - Linoleic acid (LA, 18:2n-6)
  - α-Linolenic acid (ALA, 18:3n-3)
- Medication administration
- Reverse lipophilic drug toxicity
Soybean oil-based IVLE: concerns

• Oxidative stress
  – PUFAs: lipid peroxidation
  – Insufficient antioxidants

• Inflammation
  – Pro-inflammatory eicosanoids

• Immune system dysfunction, increased risk of infections
  – Earlier studies: hyperglycemia contributed to risk
  – Now hyperglycemia more aggressively controlled: insulin

• Hepatobiliary complications
Hepatobiliary complications

- Diagnosis: clinical, biological, histological
- Liver dysfunction, parenteral nutrition-associated liver disease (PNALD), intestinal failure-associated liver disease (IFALD)
  - Transient benign increases in LFTs (AP, AST, ALT, TB, DB)
  - Cholestasis (PNAC): commonly defined as DB ≥ 2 mg/dL
  - Hepatic steatosis
  - Steatohepatitis
  - Fibrosis
  - Cirrhosis
    - Liver failure
    - Death
- Common in infants & adults receiving PN: 15-90%
  - Even if no underlying liver disease

Digest Liver Dis 2006; 38: 623-642
Hepatobiliary complications: etiology multifactorial

- Infant prematurity
- Immune hepatic function
- Lack of enteral feeding
- Prolonged use of parenteral nutrition
- Repeated episodes of infection or sepsis
- Number of laparotomies performed
- Oxidative stress
- Small bowel bacterial overgrowth

Digest Liver Dis 2006; 38: 623-642
Adv Nutr 2013; 4: 711-717
Hepatobiliary complications: etiology multifactorial

- Excess caloric intake & impaired TG secretion by hepatocytes
- Dextrose overfeeding (> 5 mg/kg/min)
- Lipid overload (> 1 g/kg/d)
- Protein malnutrition, amino acid imbalance
- Deficiencies: EFAs, carnitine, taurine, choline, glutathione
- Toxicities: manganese, copper, aluminum
- Pro-inflammatory mediators derived from n-6 PUFAs
- Phytosterols (in plant oil emulsions)
  - Downregulate suppression of bile acid synthesis
  - Reduce biliary flow

Digest Liver Dis 2006; 38: 623-642
Hepatobiliary complications: possible interventions

Non-nutritional

• Early treatment of sepsis
• Avoidance/treatment of small bowel bacterial overgrowth
  – Oral metronidazole or cyclical antibiotics
• Ursodeoxycholic acid
• Treatment of active IBD
• Treatment of underlying liver disease
• Consider prophylactic cholecystectomy
  – Long-term PN: high incidence of cholelithiasis
• Liver transplant

Nutrition 2013; 29: 356-358
Hepatobiliary complications: possible interventions

Nutritional

• Maximize enteral feeding as much as possible
• Discontinue PN
• Do not overfeed patient
• Cyclic PN
  – Mobilization of fat during fasting
• Guidelines for prevention & treatment of PNALD include:
  – Limiting glucose: total daily calorie ratio ≤ 65% or 4 g/kg/d
  – Limiting lipid: total daily calorie ratio 30% or 1 g/kg/d
  – Protein intake: 0.8-1.5 g/kg/d

Nutrition 2013; 29: 356-358
Hepatobiliary complications: possible interventions

• Modify lipid administration
  – Methods
    • Lipid restriction/discontinuation: reduce parenteral SO
    • Lipid modification: replace SO with alternate IVLEs
      – Provide n-3, MCT
      – Provide α-tocopherol
  – Effects
    • Reduce n-6, PUFAs, phytosterols
    • Reduce inflammation
    • Reduce lipid peroxidation
    • Reduce oxidative stress

Adv Nutr 2013; 4: 711-717
Low-dose SO-based IVLE: cholestasis

- Multicenter: infants, gestational age ≤ 29 weeks, < 48 hrs of age
- Control: SO (Liposyn II or Intralipid) advanced by 0.5-1 g/kg/d to target ~3 g/kg/d (n=69)
- Low-dose: max SO 1 g/kg/d (n=67)
- Analysis 62 vs 65
- Low-dose SO: did not prevent cholestasis
  - DB > 2 mg/dL: 8% (low) vs 11% (control) (P=0.6)
  - Median maximum DB: 0.6 mg/dL (low: range 0.3-9.4) vs 0.5 mg/dL (control: range 0.1-5.2) (P=0.6)
- No difference: growth velocity, mortality, major neonatal morbidities (e.g., bronchopulmonary dysplasia, late-onset sepsis, retinopathy of prematurity requiring laser)
- “this prevention strategy cannot be currently recommended for routine practice for premature neonates”
IVLEs: alternate oils

• Medium-chain triglycerides (MCTs, from coconut oil):
  – Saturated FAs, including caprylic & capric acid
  – More rapid oxidation, more immediate energy source vs SO
  – Hydrolyze & eliminate from central circulation faster vs LCTs
  – Resistant to peroxidation
  – Lack proinflammatory properties
  – Do not accumulate in liver; do not impair hepatic function
  – Cannot be sole source of IVLE
    • Combined with LCT to provide EFAs

IVLEs: alternate oils

• Olive oil:
  – n-9 MUFA: oleic acid
  – MUFAs less prone to peroxidation vs PUFAs
  – Relatively small amount of LA
  – Combine with oil containing EFAs

• Fish oil:
  – n-3 PUFAs: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)
  – Eicosanoids produced from n-3 FAs less inflammatory vs from n-6 FAs
  – Little LA & ALA
  – Contains some arachidonic acid (AA)

# Types of IVLE

<table>
<thead>
<tr>
<th></th>
<th>SO</th>
<th>OO/SO</th>
<th>*FO</th>
<th>SO/MCT/OO/FO</th>
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<tbody>
<tr>
<td>Brand name</td>
<td>Intralipid 20%</td>
<td>**Clinolipid 20%</td>
<td>*Omegaven 10%</td>
<td>SMOFlipid 20%</td>
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<tr>
<td></td>
<td>Nutrilipid 20%</td>
<td>**ClinOleic 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Soybean (100%)</td>
<td>Olive (80%) Soybean (20%)</td>
<td>Fish (100%)</td>
<td>Soybean (30%) Coconut (30%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Olive (25%) Fish (15%)</td>
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<tr>
<td>Ratio of n-6 to n-3 PUFA</td>
<td>7:1</td>
<td>9:1</td>
<td>1:8</td>
<td>2.5:1</td>
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<tr>
<td>Fat content (g/L)</td>
<td>200</td>
<td>200</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Energy (kcal/L)</td>
<td>2000</td>
<td>2000</td>
<td>1120</td>
<td>2000</td>
</tr>
<tr>
<td>α-tocopherol (mg/L)</td>
<td>38</td>
<td>32</td>
<td>150-296</td>
<td>200</td>
</tr>
<tr>
<td>Phytosterols (mg/L)</td>
<td>342 ± 5.87 439.07 ± 5.72</td>
<td>274.38 ± 2.60 226.83 ± 6.42</td>
<td>3.66 ± 0.59 207</td>
<td>178.54 ± 9.56</td>
</tr>
</tbody>
</table>

* US: special situations

** Not in US

Canadian Critical Care Nutrition
Clinical Practice Guidelines, 2015

• Withholding lipids high in soybean oil:
  – Critically ill pts who are not malnourished: consider
    • Tolerating some enteral nutrition (EN), or
    • When PN is indicated for < 10 days
  – Critically ill pts who are malnourished or requiring PN >10 days: insufficient data to make recommendation

• Withholding lipids high in soybean oil
  – Does not reduce mortality
  – Significant reduction in infections in critically ill pts
  – May reduce LOS & duration of ventilation in trauma pts

http://www.criticalcarenutrition.com/docs/CPGs%202015/10.2%202015.pdf
Accessed Sept 13, 2016
SCCM/ASPEN guidelines, 2016

“We suggest withholding or limiting SO-based IVFE during the first week following initiation of PN in the critically ill patient to a maximum of 100 g/wk (often divided into 2 doses/wk) if there is concern for essential fatty acid deficiency.”  
(Quality of Evidence: Very Low)

– “recommendation to leave off fat the first week...study was completed 20 years ago, and the results have not been replicated”

– “overfeeding may have contributed to the observed poor outcomes”

JPEN J Parenter Enteral Nutr 2016; 40(2): 159-211
Withholding IVLE first 7 days, ICU

- Retrospective study: critically ill adult pts, received PN, large academic medical center
- Withholding lipids within first 7 days of hospitalization in ICU, not associated with significant reduction in:
  - Infections (UTI, bloodstream infections, pneumonia)
  - ICU LOS
  - Total LOS
  - Mortality
- Equal incidence of hyperglycemia & severity of illness

• “The omega-3:omega-6 fatty acid ratio in Clinolipid injection has not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.”

• “There are insufficient long-term data to determine whether Clinolipid 20% can supply essential fatty acids in adequate amounts in patients who may have increased requirements.”
Not indicated for:

- Preterm infants: “Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the medical literature.” [Black box warning]
- Pediatric patients: “The safe and effective use of Clinolipid injection in pediatric patients, including preterm infants has not been established. Clinolipid injection is not indicated for and not recommended for use in pediatric patients.”
- “insufficient data to demonstrate that Clinolipid injection provides sufficient amounts of essential fatty acids in this population”

- “Pediatric patients may be particularly vulnerable to neurologic complications due to EFA deficiency if adequate amounts of EFA are not provided.”
OO/SO-based IVLE: package insert

- Pregnancy:
  - Animal reproduction studies have not been conducted
  - “Not known whether the administration of Clinolipid injection 20% to pregnant women provides adequate essential fatty acids to the developing fetus”
OO/SO-based vs SO-based IVLE: Adult, oncologic surgery

- Abdominal oncologic surgery (n=20)
  - Colon (10), gastric (9), pancreatic (1)
  - Well-nourished, GI discontinuity (12), moderately malnourished (7), severely malnourished (1)
  - Day 7 (vs Day 0): similar increase in AP & GGT, returned to normal in a few days after PN stopped
  - No difference in complications

Nutr Clin Pract 2011; 1: 61-65
OO/SO-based vs SO-based IVLE: Adult, critically ill

- MICU/SICU, Grady Memorial Hosp & Emory University Hosp
- 18-80 yrs
- 89% SICU: trauma (39.6%), major GI surg (48.4%), oncologic surg (12%)
- SO-based IVLE (n=49) vs OO/SO-based IVLE (n=51)
- Similar rates: nosocomial infections, pneumonia, wound infections, blood stream infection, UTI, ARF, ICU LOS, mortality
- No difference
  - Inflammatory markers: CRP, IL-6, TNF-α
  - Oxidative stress markers
  - Immune markers

Crit Care Med 2012; 40: 1792-1798
OO/SO-based IVLE: HPN

• 13 pts: 18-80 years; > 50% of total energy requirement provided by PN & lipid required 2 or more times per wk
• Mean period of previous PN intake: 3.8 +/- 0.8 yrs
• OO/SO-based IVLE 20% (500 ml) 2-3 times/week
  – Previously on 10% IVFE: same calories, smaller weekly volume
• 6 mos intervention, then back to pre-study lipid prescription
• 4 left trial prematurely: significant sepsis (2), abnormal LFTs & sepsis (1), withdrew consent after 15 days (1)
• 3 pts: symptomatic improvement vs habitual lipid
  – Included reduction in lipid-associated nausea & headaches
    → requested permanent change in prescription
• Appears safe & well tolerated for prolonged use in adult pts

Clin Nutr 2004; 23: 697-703
OO/SO-based IVLE: HPN

- 35-79 yrs; long term HPN (median 53 mos, range 11-177)
- 14 pts, SBS: Crohn’s disease (3), mesenteric ischaemia (6), radiation enteritis (3), chronic intestinal obstruction (2)
- Decreased α-linolenic acid significantly after 3 mo
  - Other fatty acids concentrations did not significantly differ
- Well tolerated, no adverse events
- 3 of 5 pts
  - Migraine for a long time: 100% LCTs or 50% LCTs/50% MCTs
  - Feel consistently better after introduction of OO/SO-based IVLE
- No clear cost/benefit advantage
- Suitable for long-term parenteral nutrition in stable patients

OO/SO-based IVLE: HPN

• 30 adult (> 18 yrs) home parenteral nutrition (HPN) patients
  – SBS (15), GI motility disorder (9)
  – Others (6): systemic sclerosis, chronic intestinal pseudo-obstruction, Crohn’s disease
  – Most HPN dependent > 1 year (median 1151 days)
  – None consumed relevant amounts of oral/enteral nutrition
• OO/SO-based IVLE at least 5 times/wk, at least 3 mos
  – Fat: median 0.97 g/kg/d
• No clinical or biochemical evidence of increased risk for EFAD

JPEN J Parenter Enteral Nutr 2015. DOI: 10.1177/0148607115581375
OO/SO-based IVLE: children, HPN

- 18 children, required prolonged PN (> 3 mo) to meet ≥ 80% of their protein-energy requirements
- Short bowel syndrome (n=8), intractable diarrhea (n=8), chronic intestinal pseudo-obstruction (n=4)
- 30-d equilibrium period, included 50% MCT/50% LCT IVLE, lipid intake ≥ 20% (40% maximum) of total nonprotein energy intake weekly
- 2-mo randomization period: OO/SO-based vs SO-based IVLE
- Total & LDL cholesterol, lipid peroxidation index: higher with SO-based IVLE
- OO/SO-based IVLE maintained normal EFA status
• Daily dose = 1 mL up to max of 2 mL/kg body wt (= 0.1 g to max 0.2 g fish oil/kg)
• Should not exceed 0.5 mL/kg body wt/hr (= 0.05 g fish oil/kg body wt/hr)
• Should be administered simultaneously with other fat emulsions
• On the basis of recommended total daily lipid intake of 1-2 g/kg body wt, fish oil portion should constitute 10-20% of this intake
• Duration of administration should not exceed 4 weeks
• Due to lack of experience, should not be administered in patients with severe liver or renal insufficiency
• Due to limited experience, should not be used in premature infants, newborns, infants and children
Pancreatitis: FO-supplemented PN

- 40 pt, severe acute pancreatitis, enrolled within 72 hrs after onset of severe acute pancreatitis, SICU
- PN x 5 days: glucose 3 g/kg/d (28 Cal/kg/d), AA 1.25 g/kg/d, IVLE 1 g/kg/d
- Randomized: SO (n=20) vs SO/FO (n=20)
  - FO: up to 10 g/d, 0.15-0.2 g/kg/d; n-3/n-6 ratio about 1:4
- After 5 days:
  - EPA concentration: no change with SO, significantly higher with SO/FO
  - CRP: statistically significantly lower in both groups; greater reduction with SO/FO
  - Oxygenation index: increased significantly in both groups; greater improvement with SO/FO
  - Acute renal injury: not different
  - Days of CRRT: significantly less with SO/FO (18 vs 26 days)
Pancreatitis: FO-supplemented PN

- Follow-up for 1 month after discharge:
  - No significant differences, trend toward better clinical outcome
  - Infections: 5 (SO) vs 3 (SO/FO)
  - Deaths: 2 (SO) vs 0 (SO/FO)
  - ICU LOS: 27.5 (SO) vs 21.4 (SO/FO)
  - Hospital LOS: 70.5 (SO) vs 65.2 (SO/FO)
FO: inflammatory modulation in SICU

- SICU, postop, PN > 7 d, isonitrogenous & isocaloric
- Group A (control, n=12): MCT/LCT (50:50 ratio); 10 mL/kg/d
- Group B (experimental, n=18): lipid content partially replaced by FO 0.2 g/kg/d; MCT/LCT 8 mL/kg/d, FO 2 mL/kg/d
- Infections: 41.7% (group A) vs 27.8% (group B), not statistically significant
- TG, WNL: 120 mg/dL (group A) vs 88.3 (group B), P=0.045
- Liver dysfunction: 50% (group A) vs 33.3% (group B), not statistically significant
- Inflammatory response (IL-8, IFN-γ, TNF-α): elevating trend (group A) vs significant decrease (group B)

Meta-analysis: post-surgery, FO IVLE

- Meta-analysis: 21 RCTs, 1487 pts, Europe/Asia
- Significant reduction:
  - Hospital LOS
  - Infections
  - Liver dysfunction: ALT, GGT, TB
    - After FO 0.2 g/kg/d administered IV for 5-7 days
  - Pro-inflammatory cytokines: TNF-α, IL-6, IL-2
- Significantly higher:
  - CD4+ lymphocytes
- Non-significant change:
  - Mortality
  - Postoperative medical cost
Post-op SICU: effect of FO IVLE

- Prospective, randomized, double-blinded study: 38 pts, admitted to SICU after major operations
- Group A, LCT/MCT (n=17) vs Group B, part replaced by FO (n=21); completed study (n=12 vs 18)
- Infectious complications: 5/12 vs 5/18, not statistically significant
- TG: significantly higher in Group A on POD 4, remained WNL; no statistically significant difference on POD 7
- Liver dysfunction (2x elevation from baseline): both groups
  - Higher tendency in Group A vs B (50% vs 33.3%), difference not statistically significant
- Serum inflammatory cytokine levels:
  - IL-1, IL-8, IFN-γ, TNF-α: elevating trend in Group A vs significant decrease in Group B
Meta-analysis: critically ill, FO IVLE

• Meta-analysis: 6 RCT, 390 pts
  – 1: LCT/MCT/FO vs LCT/MCT
  – 3: LCT/FO or LCT/MCT/FO vs LCT or LCT/MCT
  – 2: EN + IV FO

• FO-containing emulsions:
  – Tendency to reduce mortality & ventilation days in critically ill

• “...inadequate evidence to recommend the routine use of FO-containing emulsions in PN &/or as a therapeutic strategy in an EN-fed patient population”
Meta-analysis: critically ill, FO

- Meta-analysis: 10 RCTs, 733 pts
  - PN: LCT/MCT/FO vs MCT/LCT (3), FO/LCT vs LCT (2), FO/OO vs OO (1)
- Mortality: no significant reduction
- Infections: significantly reduced (FO IVLE)
- Mechanical ventilation: trend toward reduction in number of days (FO IVLE)
- Hospital LOS: trend toward reduction
- ICU LOS: no effects (FO IVLE)
Meta-analysis: critically ill, FO

• Higher quality trials
  – Mortality: no effect
  – Infections: statistically significant reduction
  – Mechanical ventilation: significant reduction in duration
  – Hospital LOS: significant reduction
  – ICU LOS: no effect

• “inadequate evidence to give a final recommendation on the use of FO-containing LEs as a n-6 fatty acid-reducing strategy in ICU patients who require PN &/or as a pharmaconutrient strategy in enterally or orally fed patients”
Soy-allergic: FO IVFE to treat EFAD

- July 2002: consulted for presumed EFAD, 17 yo M
- SO IVFE avoided: food allergies, including soy protein (+ skin test) & peanut protein (anaphylaxis PTA)
- EFA profile: elevated triene:tetraene ratio = EFAD
- Graded challenge to SO: difficulty breathing, tachypnea, flushing
- Corn oil applied to skin
- FO IVLE started, 0.2 g/kg/d (max approved daily dose)
  - Advanced to 0.67 g/kg/d (approx 45 mg/kg/d linoleic acid)
- After 10 d therapy:
  - Truncal folliculitis resolved, functional status improved
  - Plasma triene:tetraene ratio normalized
- Received total 57 days FO IVLE
  - Sole source of fat calories for 46 days until enteral feedings

Clinical Nutrition 2005; 24: 839-847
FO-based IVLE: infants with PNALD

- Sept 2007 to April 2013: 97 infants (2 wk to < 6 mos), PNALD
  - DB ≥ 4.0 mg/dL in absence of prior GI surgical procedure
  - DB ≥ 2.0 mg/dL with h/o GI surgical intervention or severe feeding intolerance
- D/C SO IVFE → FO IVLE (1 g/kg/d)
- 83 (86%) infants: resolution of conjugated hyperbilirubinemia
  - Median period: 40 d (3-158 d)
- 14 (14%) infants died; 13 had persistent cholestasis
- Younger gestational age infants
  - Higher degree of cholestasis
  - Longer time to resolution of cholestasis
  - Increased mortality
- Higher levels of cholestasis: longer time to resolution

Low-dose SO after resolution of cholestasis with FO

- 7 peds
- FO initiation: all had IFALD, median DB 3.5 mg/dL (3.1-7.0)
  - All had biochemical resolution of cholestasis (TB < 2 mg/dL) for 20.7 mos (7.5-24.2)
  - Transitioned to low-dose SO (1 g/kg/d) after median 20.7 mos (8.5-26.6) of FO
- FO or SO, 1 g/kg/d: not associated with biochemical EFAD
- 6 of 7: preserved biochemical resolution of cholestasis & growth

J Pediatr Gastroenterol Nutr 2015; 60: 375-377
Low-dose SO after resolution of cholestasis with FO

• 1 of 7:
  – Before initiating FO, liver bx: marked fibrosis with portal-to-portal bridging
  – FO x 28 mos → TB < 2 mg/dL
  – Low-dose SO x 4 mos
    • Cholestasis: peak TB 6.6 mg/dL, DB 5.0 mg/dL
    • Repeat bx: marked fibrosis with IFALD findings
  – Reinitiated on FO: DB resolved after 8 mos
  – Remained on FO
IFALD: FO monotherapy x 6 mos

• 10 pts (2 wk-18 yr), IFALD, DB ≥ 2 mg/dL (2 consecutive measurements separated by at least 1 wk)
  – FO: 0.5 g/kg/d x 2 d, then 1 g/kg/d x 24 wk
  – Persistent or recurrent cholestasis after 24 wk of FO: could receive 2 more courses, max 48 additional wks
  – 20 historic controls: variable SO doses
• DB, TB, AST, ALT: decreased significantly over time
• Resolution of cholestasis
  – 11.5 wk (FO; 2.4-18 wk) vs 24 wk (SO; 5.4-24 wk)
  – 75% by 17 wk FO monotherapy
• None developed EFAD

IFALD: FO monotherapy x 6 mos

- 6/8: transitioned to SO 0.9 g/kg/d (0.6-1 g/kg/d)
  - Restart SO & dose at discretion of primary medical team
- End of follow-up, median 1.9 yr (1-2 yr)
  - 1: free of cholestasis, intestinal adaptation after additional 12 mos PN + SO
  - 1: cholestasis/IFALD, requiring multivisceral transplant
  - 3/7: continued PN + mean SO 1 g/kg/d (0.5-1.3 g/kg/d)
    - Continued normal DB
    - Decreased median ALT & AST at end of follow-up period (32 & 33) vs at FO termination (67 & 81)

PN-dependent adult, FO IVLE: decrease liver steatosis & inflammation

- 59 yo F, HPN since 1990, SBS due to intestinal resections for Crohn’s disease (residual bowel: jejunum 60 cm, left colon)
- LFTs normal until 2003
- US: steatosis of moderate degree (2004); severe degree (2005)
- SO IVLE decreased from 6 to 3 per wk, then replaced with OO/SO
- No improvement in liver steatosis & LFTs
- June 2008: liver bx
- July 2008, started FO (7.5 g/d, 0.2 g/kg/d, 5-7 d/wk) + OO/SO
- Before FO: liver histology showed NASH, grade 2 steatosis & inflammation, stage 3 fibrosis
- After FO x 8 mos: grade 1 steatosis & inflammation; stage 3 fibrosis
PN-dependent adult, FO IVLE: reversal of chronic liver disease

- 50 yo F, acute abdomen with mid-gut volvulus, 2005
- s/p extensive surgical resection of small intestine, remaining 10 cm of jejunum anastomosed to transverse colon; cholecystectomy
- Stable PN formula over 5 yr, with SO-based IVLE 40 g/d (0.83 g/kg, 3:1 admixture)
- Within 1 yr postop: AST/ALT ~ 2x upper limit, AP 2-3x upper limit, bilirubin normal
- US: steatosis of liver, no evidence of portal HTN
- Ursodeoxycholic acid 15 mg/kg: some improvement of LFT, particularly AP

JPEN 2013; 37: 274-280
PN-dependent adult, FO IVLE: reversal of chronic liver disease

- Subsequent 5.5 yrs, occasional hospitalizations for central venous catheter infections
- Beginning of 2010: malaise, fatigue, nausea, vomiting, severe diarrhea; LFTs worsened (AST/ALT 5-6x control, AP 2x control), jaundice with peak TB 14.3 mg/dL
- US: steatosis of liver, no evidence of biliary obstruction or portal HTN
- Dec total cals (22 Cal/kg), 40 g lipid once a week: wt loss
- Liver bx: moderate to severe hepatocanalicular & ductal cholestasis, portal expansion with bile ductular proliferation, mild acute on chronic inflammation

JPEN 2013; 37: 274-280
PN-dependent adult, FO IVLE: reversal of chronic liver disease

- Nov 2010: started FO IVLE, 45 g over 16 hr, 5x weekly
- Within 4 wk: improved energy, improved appetite, decreased RUQ abd pain; resolved N/V/D
- 5 wk: TB decreased from 12.4 → 4.2 mg/dL; CRP decreased from 23 → 4.1 mg/L; both normalized
- After 3 mos of FO IVFE: all symptoms absent
- After 16 mos tx: asymptomatic, weight gain
  - CRP: 23.0 → 2.9  
  - Prealbumin: 11.0 → 16.6  
  - Albumin: 2.4 → 3.3  
  - AST: 225 → 87  
  - ALT: 124 → 93  
  - TB: 12.4 → 0.9
Adult, FO IVLE: reduce bx-proven PNALD

• 15 adult pts (20-45 yr, 9 M, 6 F), SBS (SB 100 cm or less), cholestasis (DB ≥ 2 mg/dL)
• MCT/LCT → MCT/LCT + FO (up to 10 g/d, about 0.15-0.2 g/kg), at least 1 mo
• Median duration of PN before initiation of FO = 2 mos (2-19 mos)
• After 1 mo of mixed lipids: 12/15 DB normalized within 4 wks & DB markedly decreased over time in study; also marked decrease in ALT
• No evidence of coagulopathy; slight increase in INR (P=0.500)
Adult, FO IVLE: reduce bx-proven PNALD

- 11/15: liver bx pre-therapy & post-therapy
  - Portal inflammation infiltration with granulocytes & neutrophils all cases, varying intensity
  - Cholestasis (including hepatocellular cholestasis &/or canalicular cholestasis): varying degrees of severity in most cases
  - Other features of PNALD included steatosis & fibrosis (marked bridging)
- Before starting FO: cholestasis & inflammation present in most cases
- After 1 month of treatment: markedly decreased degree of cholestasis & inflammation
SO/MCT/OO/FO-based IVLE: package insert

• “The omega-3:omega-6 fatty acid ratio & Medium Chain Triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions”
• “Monitoring patients for signs and symptoms of EFAD is recommended.”
• “There are insufficient long-term data to determine whether Smoflipid can supply essential fatty acids in adequate amounts in patients who may have increased requirements”
• “contains soybean oil, fish oil, and egg phospholipids, which may cause hypersensitivity reactions. Cross reactions have been observed between soybean and peanut oil.”
SO/MCT/OO/FO-based IVLE: package insert

• Not indicated for:
  – Preterm infants: “Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the medical literature.” [Black box warning]
  – Pediatric patients: “The safe and effective use of Smoflipid in pediatric patients, including preterm infants has not been established.”
  – “insufficient data from pediatric studies to establish that Smoflipid provides sufficient amounts of essential fatty acids in pediatric patients”
    • “Pediatric patients may be particularly vulnerable to neurologic complications due to EFA deficiency if adequate amounts of EFA are not provided.”
SO/MCT/OO/FO vs SO: postoperative, multicenter

• Prospective, randomized, double-blind, 18 European center study
• 249 pts randomly allocated; SO/MCT/OO/FO 20% vs SO IVLE: 1.5 g/kg/d, continuously over 24 hours, over 5 postoperative days
  – All received at least one dose (ITT population)
  – 50 excluded from analyses: SO/MCT/OO/FO (n=27), SO (n=23)
  – Per-protocol population: SMOF (n=99), SO (n=100)
• Inclusion: immediate postoperative period after elective abdominal or thoracic surgery; aged 18 or older; indication for TPN over at least 5 days
• AST, ALT, AP: more above normal with SO
• Per-protocol pts, SO/MCT/OO/FO: tendency for shorter LOS (15.7 vs 17.8 days)
  – No difference in LOS for ITT population

Ann Nutr Metab 2006; 50: 253-259
SO/MCT/OO/FO vs SO: postop

• Randomized, double blind study, 2 centers, 33 pts, over 5 postoperative days following major abdominal surgery
• SO/MCT/OO/FO 20% vs SO 20%: 1.5 g/kg/d
• After 6 days:
  – Contents of phospholipid derived total n-3 FA (EPA & DHA) were higher; linoleic acid, AA & total n-6 FA were lower
  – Ratios of n-3/n-6 FA & EPA/AA: profoundly elevated with SO/MCT/OO/FO
  – LTB5 release enhanced & liberation of LTB4 lowered with SO/MCT/OO/FO
    • Ratio of LTB5/LTB4 was increased vs unchanged in control group
  – Plasma α-tocopherol significantly higher with SO/MCT/OO/FO vs SO
  – Reduced length of stay with SO/MCT/OO/FO vs SO (13.4 vs 20.4 days, p<0.05)

Eur J Nutr 2006; 45: 55-60
SO/MCT/OO/FO vs SO: postop ICU pts

- Prospective, randomized, double-blinded study
- 90 consecutive pts admitted to SICU after major operations
- PN for not less than 7 days postoperatively, fat content did not exceed 1.5 g/kg/d
  - Group 1: SO (n=42)
  - Group 2: SO/MCT/OO/FO (n=41)
- IL-6: significantly lower on day 4 & 7, SO/MCT/OO/FO vs SO
  - Reduced inflammatory response
- Ventilator days, ICU LOS, hospital LOS, 1 wk mortality, 1 mo mortality: reduced, not statistically significant
- Vital signs, cholesterol, TG, liver enzymes: no significant differences
Meta-analysis:
SO/MCT/OO/FO for surgical patients

- 6 RCTs, SO/MCT/OO/FO vs other IVFEs:
  - SO (3)
  - OO/SO (1)
  - LCT/MCT (2)
- Immediate postoperative period after elective abdominal or thoracic surgery, 4-6 days
- 306 patients total; 10-100 pts/treatment group
- SO/MCT/OO/FO vs SO:
  - Decrease AST, ALT, GGT, AP: may be less toxic to the liver
  - Lower change in TG
SO/MCT/OO/FO vs SO: multicenter, 4 weeks

- Randomized, controlled, double-blind: 11 centers, 7 countries (Australia, Denmark, France, Israel, Netherlands, Poland & United Kingdom)
- Oct 2007-Oct 2008:
  - SO/MCT/OO/FO (n=34) vs SO (n=39)
  - 1-2 g/kg/d (5-10 mL/kg/d), 5-7 days/wk, 10-24 hr infusion
  - All-in-one solutions, 4 wks
- Eligible: 8-85 yrs, unable to sustain adequate oral/enteral food intake for at least 4 wks & in need of PN

Clinical Nutrition 2013; 32: 224-231
SO/MCT/OO/FO vs SO: multicenter, 4 weeks

- ALT, AST, TB: decrease with SO/MCT/OO/FO vs slight increase with SO (but still within reference range)
  - Mean concentrations significantly lower: SO/MCT/OO/FO
- Cytokine markers of inflammation (IL-6, sTNF-RII, CRP): similar at baseline & at end of study; no change during study period
- Serum α-tocopherol levels: significantly higher with SO/MCT/OO/FO vs SO by week 2 & remained until end of study
- EPA & DHA: significantly increased with SO/MCT/OO/FO; lower n-6/n-3 ratio in plasma & in RBC with SO/MCT/OO/FO
Adult PNAC:
OO/SO to SO/MCT/OO/FO

• 43 yo M: c/o acute, severe abdominal pain; h/o vascular disease
• OR: necrosis of SB from duodenojejunal flexure to distal terminal ileum consistent with mesenteric infarction ⇒ SB resection ⇒ duodenostomy, most of colon intact, not in continuity
• 6 months later: jaundice with cholestatic liver blood tests; weight decreased to 43 kg (discharge 56 kg)
• Liver bx: severe acute cholestasis & minimal steatosis without steatohepatitis; portal tracts showed marked bile ductular proliferation & inflammation; chronic cholestasis; moderate portal fibrosis – all consistent with PNALD
Adult PNAC: 
OO/SO to SO/MCT/OO/FO

• Reduction in PN lipid content & trial of N-acetylcysteine: no improvement in liver function
• Portal HTN & bled from gastric varix, required endoscopic hemostasis
• 4 months later, deteriorating liver function:
  – Changed from 500 mL once weekly of OO/SO 20%
  – To SO/MCT/OO/FO 20%
• At same time, stoma stenosis
  – Revised
  – Increase oral fluids

Frontline Gastroenterology 2012; 3: 94-97
Adult PNAC: OO/SO to SO/MCT/OO/FO

- 8 wks later, return to clinic:
  - Less jaundiced, LFTs improved
- Gradual normalization of serum bilirubin, transaminases & alkaline phosphatase levels
- Albumin: from nadir of 12 g/L to 37 g/L
- Repeat upper GI endoscopy: resolution of gastric varices
- Serial fibroscan assessments: progressive fall in liver stiffness after introduction of SO/MCT/OO/FO
- Multi-visceral transplant of stomach, liver, duodenum & pancreas
  - Discharged 12 weeks postoperatively
  - Nutrition: nasojejunal feeding

Frontline Gastroenterology 2012; 3: 94-97
SO/MCT/OO/FO: premature neonates

- 53 premature neonates, at least 1 dose (ITT population)
- Randomized: SO/MCT/OO/FO (n=26) vs SO (n=27), x 7-14 d
- 1.0 g/kg/d (D 1-3) → 2 g/kg/d (D 4) → 3 g/kg/d (D 5) → 3.5 g/kd/d (D 6+)
  - TG > 300 mg/dL: reduce by steps of 0.5 g/kg/d
- Most did not require PN beyond 3rd wk of life
- Enteral intake of lipid permitted if appropriate & documented
- Per-protocol analysis: n=23 & n=23
- Body weight & height: significantly increased vs baseline in both groups
- TG: increased in both groups (D 8) vs baseline; significant in test group only; not different between groups
- TB: decreased significantly with SO/MCT/OO/FO after 7-14 days vs not with SO
- DB: slight decrease with SO/MCT/OO/FO vs significant increase with SO
PN-associated jaundice: SO to SO/MCT/OO/FO

• Children who developed cholestatic jaundice (bilirubin persistently > 70 umol/L, 4 successive weeks) due to PNALD
• Protocol of SO → SO/MCT/OO/FO (n=8, median age 30 wks [16-164]) vs historic cohort (no change, n=9, median age 24 wks [8-64])
  – 6 mo follow-up
  – PN reduced stepwise if improved EN tolerance permitted
  – Average 0.3 g/kg/d FO
• Median bilirubin: decreased by 99 umol/L (SO/MCT/OO/FO) vs increased by 70 umol/L (SO)
• Total resolution of jaundice: 5/8 (SO/MCT/OO/FO); 2/9 (SO)

JPGN 2012; 54: 797-802
Meta-analysis: children receiving PN, SO vs combination (3 or more oils) IVLE

- Meta-analysis, 9 studies, 361 pts
  - SO/MCT/OO/FO (6); SO/OO/FO (2); MCT/SO/FO (2)
  - Gestational age < 40 wks (6 studies); all infants < 12 mos old
- Premature infants, infants with SBS, infants undergoing heart surgery, children receiving long-term PN, children who developed PNALD
- Hospitalized infants/children (8); children receiving HPN (1)
- Lipids: 1.6-3.5 g/kg/d; duration of PN: 7 days to 17 months
- Some used EN also
- Total bilirubin: decreased with combination LE vs SO
- Triglyceride: no significant difference
- Infection, adverse events, death: no statistically difference
- “Combination LEs in children appears to be a safe alternative to standard LEs”

Reversal of IFALD: SO/MCT/OO/FO to FO

- SO/MCT/OO/FO, primary IVFE, peds PN pts since 2011
- IFALD: DB > 2 mg/dL, 2 consecutive wks or more
- SO/MCT/OO/FO 3 g/kg/d (0.45 g/kg/d FO) → 2 g/kg/d → 1 g/kg/d → switched to FO 1 g/kg/d
- 11 mo F: DB decreased after 60 days; IFALD completely resolved after 90 days
  - FO x 26 wk → switched back to SO/MCT/OO/FO 2 g/kg/d: DB remained WNL
- 1 mo M: DB increased during first month, then gradual decrease; IFALD completely resolved after 5 months
  - Switched back to SO/MCT/OO/FO 2 g/kg/d: DB WNL

Meta-analysis: critically ill, alternative oil-based IVLE

- Meta-analysis, 12 RCTs, 806 critically ill adults
- SO-sparing strategies (reduce n-6) vs SO-based IVFE in PN
- Reductions – not statistically significant:
  - Mortality (RR 0.83; P = 0.20)
  - Ventilation days (WMD -2.57; P = 0.09)
  - ICU LOS (WMD -2.31; P = 0.13)
- 5 RCTs, ICU-acquired infections, no effect (RR 1.13; P = 0.35)
- No clear superiority of one alternative vs another
- ? Specific lipid components or reduction in soy lipid exposure
- “unable to define best n-6-sparing strategy in critically ill”

Intens Care Med 2013; 39: 1683-1694
Canadian Critical Care Nutrition
Clinical Practice Guidelines, 2015

• LCT reducing strategies (SO sparing strategies)
  – No effect: mortality or infections in critically ill adults
  – Trend towards reduction: hospital LOS, ICU LOS & duration of ventilation

• OO containing emulsions (vs LCT)
  – No effect on mortality or ICU LOS
  – May be associated with
    • Trend towards increased infections
    • Significant reduction in duration of ventilation

• When PN with IV lipids is indicated
  – Consider: reduce load of n-6 FAs/SO emulsions

• Type of lipids: insufficient data to make recommendation

http://www.criticalcarenutrition.com/docs/CPGs%202015/9.2%202015.pdf
SCCM/ASPEN guidelines, 2016

• “Alternative IVFEs may provide outcome benefit over soy-based IVFEs; however, we cannot make a recommendation at this time due to lack of availability of these products in the United States.

• When these alternative IVFEs (SMOF [soybean oil, MCT, olive oil, and fish oil emulsion], MCT, OO, and FO) become available in the United States, based on expert opinion, we suggest that their use be considered in the critically ill patient who is an appropriate candidate for PN.”
FO-based IVLE, multicenter: doses & responses

- 661 pts, 82 German hospitals, max 10 pts recruited per study center
- TPN including FO for ≥3 days, regardless of underlying diagnosis
- SO + FO supplement: dosage of FO at discretion of MD
- FO > 0.05 g/kg/d: significant reduction of ICU LOS, hospital LOS
- Necessity for antibiotic treatment: significantly higher with doses of <0.15 g/kg/d vs 0.15 & 0.20 g/kg/d
- Survival significantly improved: 0.1-0.2 g/kg/d vs <0.05 g/kg/d
- Mortality significantly reduced: with abdominal sepsis, multiple trauma, & severe head injury
- No significant effect: postoperative surgical pts & cases of nonabdominal systemic inflammatory response syndrome & sepsis

Crit Care Med 2006; 34: 972-979
Meta-analysis: elective surgery & ICU pts, n-3 enriched PN

- Meta-analysis: 23 studies, 1502 patients
  - 13: admitted to ICU (762 patients)
  - 10: major abdominal surgery & not admitted to ICU
- n-3 PUFA-enriched vs SO, LCT/MCT, or OO/SO:
  - Mortality rate: no statistically significant difference
  - Infection rate: significant reduction
  - ICU LOS, hospital LOS: statistically & clinically significant reduction
  - Markers of inflammation
    - IL-6: significantly greater reduction
    - Leukotrienes: significant increase in leukotriene B5 (LTB5), decrease in LTB4, & significantly ameliorated LTB5:LTB4 ratio
    - Serum ALT & AST: significant reduction
- Dose at least, must exceed 0.1-0.15 g/kg/d fish oil

Critical Care 2012; 16: R184
Hospitalized adult: FO dose & LFT

- Retrospective study: 53 pts, median age 68 yr (24-90), received FO supplementation in PN, no enteral nutrition or oral food; PN median 19 (7-75) days
- Most frequent dx: digestive neoplasm
- Main indication for PN: paralytic ileus or intestinal failure
- Lipids: OO/SO, SO/MCT/OO/FO, FO
- Protocol: max dose 1 g/kg/d; reduced with hypertriglyceridemia
  - Inflammatory state classified: CRP, prealbumin
    - Presents inflammatory state: SO/MCT/OO/FO
    - High inflammatory state: OO/SO + FO (most common used)
  - Hypertriglyceridemia: only FO
Hospitalized adult: FO dose & LFT

- 23 septic pts:
  - 22 presented highest GGT, AP or ALT during septic event
  - 23 had highest TB simultaneously with sepsis
- Pts with higher decrease of AP: higher doses of FO
  - Highest decrease of AP: mean total dose = 8.96 g/kg
- Amount of FO related to decrease in GGT, AP, ALT
- Increases in TB associated with longer ICU stay
- “it would be of interest to use higher doses of FO in those adult patients who develop liver parameter alterations during hospitalization with PN treatment”
FO IVFE & LFTs: hospitalized adults

- Four types
  - OO/SO: moderate metabolic stress
  - SO/MCT: severe metabolic stress & hypertriglyceridemia
  - SO/MCT/OO/FO: severe metabolic stress & high levels of inflammatory response
  - FO in combination with other IVFEs: severe inflammatory response required higher FO doses
- Maximum FO supplementation: 23% of total lipid intake
- With FO: no significant increases for GGT & AP
  - Without FO: significant increase for GGT & AP
- Higher CRP associated with significant increase of GGT & AP
- Received higher proportion of FO: better values for all LFTs
- “challenge would lie in knowing which hospitalized adult patients, under what conditions and at what dose should receive FO for the prevention and treatment of LFT alteration”

Clinical trial

• Fish OIL optimal dosE Determination study (FOILED; ClinicalTrials.gov NCT01146821)
  – Evaluating the safety & efficacy
  – IV FO doses of 0.20 g/kg & 0.50 g/kg, vs control group
  – Critically ill patients with sepsis
PNALD in infants, IVLE: summary

- Increased exposure to SO IVFE contributes to development & progression of PNALD
- Parenteral lipid management
  - Lipid restriction: ≤ 1 g/kg/d (from 2-3 g/kg/d)
    - Some: cholestasis resolved
    - Some: no impact on incidence of cholestasis, PNALD
    - Risk: EFAD development, growth failure
    - Long-term restriction: unknown consequences on brain & cognitive development
  - Lipid replacement: eliminate SO, replace with alternate lipid source
    - FO: resolution of biochemical cholestasis; significant decreases in morbidity & mortality; restricted to compassionate use protocol
    - FO: monotherapy does not lead to EFAD development

Am J Clin Nutr 2016; 103(Suppl): 629S-634S
Omegaven – How To Obtain

Omegaven 10% Emulsion is a fish oil emulsion administered intravenously in patients who require parenteral nutrition supplementation with long chain omega-3 fatty acids, especially eicosapentaenoic and docosahexaenoic acid, when oral or enteral nutrition is impossible, insufficient or contraindicated. Omegaven is not approved for marketing in the United States but is approved in Germany. Fresenius Kabi, the manufacturer, has been supplying it for expanded access in the United States. Physicians interested in obtaining expanded access for Omegaven must submit an investigation new drug application (IND). An IND is a request for FDA authorization to administer an investigational new drug (e.g., Omegaven) to humans. Such authorization would allow the importation, interstate shipment, and administration of the drug even though it is not approved for sale in the U.S.

Single Patient IND (SPIs)
Physicians can obtain Omegaven for a single patient by submitting a Single Patient IND (SPI) application to the FDA. FDA generally responds to new Single Patient IND requests within a week or less. Every effort will be made to meet a physician’s request for expedited review. Contact the DDI (below) to request the Omegaven Single Patient IND Packet.

Emergency IND (EINDs)
Physicians may seek emergency access to Omegaven for an individual patient (see 21 CFR 312.310(d). An emergency IND (EIND) is applicable when the patient requires treatment before a written submission can be made. Contact DDI (below) to request the Omegaven Emergency IND Questionnaire.

Division of Drug Information (DDI):
toll free (855)-543-3784 or (301) 796-3400
e-mail: mailto:druginfo@fda.hhs.gov
Predictors of failure of FO: IFALD in children

- Jan 2004 to Dec 2014: 182 pts treated with FO monotherapy 1 g/kg/d
- Resolution of cholestasis (sustained DB < 2 mg/dL): 86%
- Treatment failure (liver transplantation or death while DB > 2 mg/dL): 14% (4% transplant, 10% mortality)
  - Lower birth weight
  - Older (≥ 16 wk) at FO initiation
  - More advanced liver disease at FO initiation
  - History of GI bleeding
  - Presence of non-GI comorbidities
  - Mechanical ventilation at FO initiation
- Recommend
  - Early FO initiation once biochemical cholestasis is detected in PN-dependent pts
  - All PN-dependent pts with IFALD: refer to specialized centers

Am J Clin Nutr 2016; 104(3): 663-670
FO: hepatic explant pathology

- 7 peds: liver+intestinal transplant
  - Mean duration of FO @ 1 mg/kg/d = 16.1 mos before transplant
  - Median TB 6.9 mg/dL at start of FO → 0.7 mg/dL at transplant
  - No significant improvements in ALT, Alb, or Plt
- Control: 11 peds, liver+intestinal during same period
  - SO @ 1-3 g/kg/d
- At transplant: mean TB 0.9 (FO) vs 6.5 (SO)
  - No significant difference: ALT, Plt, Alb
FO: hepatic explant pathology

• No liver bx before transplant
• All 7 in FO group:
  – Stage 3 or stage 4 fibrosis
  – Inflammation & other typical features of end-stage PNALD of childhood: consistently mild or absent
• Replacement of SO with lower dose of FO
  – Resolution of cholestasis
  – Decreased inflammation
  – Continued fibrosis

World J Gastroenterol 2015; 21(17): 5115-5118
Case study

- 64 yo F
- 2008: resection, abd mass & mesenteric mass
- Dx: Diffuse large B cell lymphoma
- Total enterectomy, venting G-tube ⇒ Short Bowel Syndrome
- TPN: Dex 350 g, AA 92 g; 250 mL 20% SO BIW
What types of individuals in your practice might benefit from the use of specific types of Intravenous Lipid Emulsions (IVLEs)?

When would you use the specific products?
IVLE summary

• Content: type of FAs, dose of FAs, phytosterols, antioxidants
• Potential complications
  – Essential fatty acid deficiency
    • Clinical or biochemical
  – Hepatobiliary complications
  – Effect on infection, ventilator days, LOS, mortality
  – Neurologic
• Population
  – Allergy to soybean
  – Inflammation: surgery, trauma, critically ill, cancer
  – Growth & development: neonate, pediatric
  – Long-term HPN-dependent
• Duration of therapy
• Timing
Self-assessment question # 1

• Olive oil is a rich source of ____.
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 2

• Which of the following products contains the lowest amount of phytosterols?
  A. Clinoleic
  B. Intralipid
  C. Omegaven
  D. SMOFlipid
Self-assessment question # 3

• For individuals who develop parenteral nutrition-associated cholestasis, the current practice is to reduce the amount of ____ administered.
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 4

• Individuals with significant inflammation may benefit the most from the use of intravenous lipid emulsions which contain ____.
  A. Medium-chain triglycerides
  B. Omega-3 fatty acids
  C. Omega-6 fatty acids
  D. Omega-9 fatty acids
Self-assessment question # 5

• Which micronutrient is added to intravenous lipid emulsions for its antioxidant effects?
  A. Selenium
  B. Vitamin A
  C. Vitamin C
  D. Vitamin E
Questions?

Thank you